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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,421	03/25/2005	Andreas Meyer	PC/4-32584A	8057

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,421	MEYER ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33* is/are rejected.

7)☒ Claim(s) *31 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/17/2009 has been entered.

Response to Arguments

2. Applicants' arguments, filed 2/17/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments with respect to the rejection under 35 USC 112, 1st paragraph have been fully considered but they are not persuasive:

Claims 27-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues claim 32 has been amended to recite pitavastatin Ca-salt, that the inner phase comprises 5% by weight of composition HPMC (3cps) and 18.75% weight of composition HPMC; HPMC in the outer phase is 100'000 cps and the outer phase comprises 0.5% by weight of composition magnesium stearate; with specific support provided at Example 4 on pp. 3-4. This is not persuasive; Example 4, of the paragraph bridging pp. 29-30, requires 18.75% HPMC (100 cps) in the inner phase in addition to the 5% HPMC (3 cps); the 18.75% HPMC (100 cps) is not recited in the claim. Therefore, Example 4 does not provide written support for claim 32.

Applicant further argues that p. 14, 2nd full paragraph and final paragraph provides support for claim 27 as amended. This is not persuasive; lines 7-18 of p. 14 do not support claim 27 (or claims dependent thereon) for at least the following reasons: 1) The second paragraph of p. 14 (lines 7-14 do not recite any spatial locations (inner phase or outer phase); if taken with lines 15-18, which does disclose two phases, lines 7-18 do not disclose an amount of flow agent (0.1-2% is required in the claim), and line 18 requires a lubricant, not recited in the claim; 2) The disclosure at this location is not limited to pitavastatin, but generally recites a "drug substance", when taken with lines 19, the preferred drug is pitavastatin Ca-salt, which is a different compound than pitavastatin; 3) The amount of matrix former is specifically limited to HPMC in lines 11-12, but the claims are broader, reciting "matrix former" in claim 27 and "hydrophilic polymer" in claim 28, and non-HPMC options recited in claim 33 are not disclosed in this location.

Specification

4. The abstract of the disclosure is objected to because commas are missing after "binder" on line 16 of page 14, and after wt% on line 24; commas that are used to mark decimal points in numerical values are improper, and should be changed to periods (e.g., in lines 25-28 of p. 14; lines 12 and 18 of p. 15; lines 5, 11, 12, 17 and 23 of p. 16, etc.) and spaces whould be removed between words and the commas or periods that follow, such as at p. 14, lines 16, 18. Correction is required. See MPEP § 608.01(b).

Claim Objections

5. Claims 31-32 are objected to because of the following informalities: the term silicium is a misspelling of silicon. Appropriate correction is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alberts et al. (EP 0 465 096 A1; 1992; cited in a prior office action); Kanjinami et al. ("NK-104: a novel synthetic HMG-CoA reductase inhibitor"; 2000; Expert Opinion on Investigational Drugs; 9(11); 2653-2661); Maggi et al. ("Formulation of biphasic release tablets containing slightly soluble drugs"; 1999; European Journal of Pharmaceutics and Biopharmaceutics; 48: 37-42); and Tanizawa et al. (US 2004/0018234 A1; priority date 2002 Jun; cited in a prior Office Action).

Alberts teaches compositions with an HMG-CoA reductase inhibitor in sustained-release formulations, which affords equivalent or improved reduction of plasma cholesterol levels, while significantly reducing the amounts of HMG-CoA reductase inhibitor circulating in the bloodstream, compared to a rapid release dosage form (abstract; p. 2, lines 21-26; p. 3, lines 7-10); controlled delivery devices include dissolution controlled matrices and erodible/degradable matrices (p. 2, lines 27-29); various statins are taught as HMG-CoA reductase inhibitors (p. 2, lines 5-8); sustained

release pharmaceutical compositions containing an HMG-Co reductase inhibitor in the amount of 4-17 weight percent and a hydroxypropyl methyl cellulose, such as methocel K100M (a 100,000 cps HPMC) in the amount of 19-43 weight percent of a unit dosage (p. 3, lines 33-42); coated tablets are taught with a matrix-delivery system, containing simvastatin, in amounts ranging from 10-40 g, Avicel PH101 and lactose, a Methocel (microcrystalline cellulose) in amounts in an inner phase and a film coat (outer phase) comprising HPMC (6 cps) and HPC (examples 11-16); magnesium stearate and ascorbic acid are taught (stabilizers). Alberts does not teach pitavastatin along with HPMC in an outer phase in the same composition, or the Ca salt of pitavastatin, the elected stabilizer potassium bicarbonate, the amounts of claim 27, or the specific combination of claim 32.

Kanjinami teaches NK-104 (pitavastatin), a powerful statin, has the potency equivalent to that of atorvastatin, which is safe and well-tolerated in treatment of patients with hypercholesterolaemia, the cytochrome P450 system only slightly modifies NK-104, which suggests the clinical advantage of this agent, because the prevalence of clinically significant interactions with a number of other commonly used drugs can be considered to be extremely low (abstract); NK-104 taught is the monocalcium salt (pitavastatin Ca salt; p. 2654, section 2); partition coefficients (in n-octanol/phosphate buffer, pH 7.0) is 31.7, similar to atorvastatin (indicating the compound is lipophilic; p. 2654, section 2).

Maggi teaches a biphasic release system for slightly soluble drugs; two components are taught, one of which is an extended-release HPMC matrix, where

different HPMC concentrations of 10, 16 and 22% are used and viscosity grades that includes Methocel K100M (a 100,000 cps viscosity) were used to obtain different release rates of the drug from the extended-release layer with slightly soluble model drugs, an increase in the percentage and viscosity grade of HPMC in the extended release layer leads to a decrease in the drug delivery rate and produces a wide range of different release rates from only a few hours up to 24 hours (abstract); excipients used includes colloidal silicon dioxide at 0.4 %, and magnesium stearate at 1.4% (p. 38, right, 4th paragraph, Table 1); various amounts of HPMC and mannitol were mixed, to vary the relative HPMC amount, while keeping the matrix weight and surface area constant

Tanizawa teaches compositions that contain pitavastatin or a salt of pitavastatin in a controlled release pharmaceutical composition (abstract); pharmaceutical compositions containing pitavastatin and at least two layers, which release the drug rapidly in the stomach, and an enteric component, which releases a portion of the drug slowly (abstract); the Ca-salt of pitavastatin (paragraph 0015); pitavastatin exhibits a high absorption in the large intestine as well as the duodenum, so that controlled release can attain a virtually identical level of boiavailability as ordinary preparations of the same dose (paragraph 0014); in one preferred embodiment a pitavastatin-containing composition is coated with the sustained release component, such as a cellulose derivative and silicones (paragraph 0025); cellulose derivatives include HPMC (paragraph 0027); HPMC as a sustained release component (matrix former) is present in at least the outer phase, as well as the inner phase (paragraph 0032, 0036, 0041, 0042, example 1); lubricants may be added to the enteric composition (paragraph

0046); pitavastatin doses include the preferable range 1-32 mg (paragraph 0065) and 16 mg (example 1, Table 2); HPMC is present at 9.375 wt % (Table 2); magnesium alumino metasilicate (stabilizer) is taught at 1.25 wt % (Table 2); more than one type of matrix former component is taught (Tables 5, 7), these components are distinct and, absent evidence to the contrary, have different viscosities; additional diluents to the pitavastatin include microcrystalline cellulose (paragraph 0017); in order to enhance the time-lapsing stability of pitavastatin a basic substance which can elevate pH of an aqueous solution to 6.8 or higher is added, basic substances include antacids such as potassium phosphate and sodium hydrogen carbonate (paragraph 0023); magnesium stearate is included at 0.56% (Example 8), and in smaller and larger amounts (Examples 9 and 6); examples of tablets include nucleated core-shell tablets (paragraph 0050).

It would have been obvious to one skilled in the art at the time of the invention to prepare a core containing pitavastatin Ca, microcrystalline cellulose, potassium bicarbonate and HPMC, then to coat the inner phase with an outer phase containing HPMC (Methocel K100M, 100,000 cps), silicon dioxide colloidal, and magnesium stearate, into a sustained release pharmaceutical composition. The motivation to include pitavastatin Ca, would have been for the specific benefits taught by Kanjinami; the motivation to include microcrystalline cellulose in the core would have been as a diluent material, as taught by Tanizawa; the motivation to include potassium bicarbonate would have been the substitution of the potassium cation from potassium phosphate combined with the anion from sodium hydrogen carbonate, to give

potassium bicarbonate, with the expectation that the compound would have provided pH elevation to protect the pitavastatin from the acidic environment of the stomach, as indicated by Tanizawa; the motivation to use HPMC at 100,000 cps in the outer phase, would have been the expectation that optimizing the amount would have been able to control the release rate of the drug, suggested by Maggi; the motivation to include silicon dioxide colloidal and magnesium stearate is for their lubricating ability and suitablilty in such formulations, so indicated by their inclusion in the Maggi formulations, as well as within the teachings of Tanizawa. It would have further been obvious to optimize the amounts of each of these components to optimize the rate of drug release, amount of drug dosed, protection of potassium bicarbonate and lubrication of tablet presses. Such routine optimization would have given amounts within the amounts of claim 27 and the amounts of claim 32, absent evidence to the contrary.

As pointed out in MPEP 2144.05 II, generally differences in concentration of temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is

(571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614